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# A family of PP2 phosphatases in and parasitic protozoa: reply.

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## How does the Sparganosis Occur?

Several species of helminths can absorb arachidonic acid (AA) from their environment and metabolize it to form prostaglandins<sup>1</sup>. *Schistosoma mansoni* cercariae can form prostaglandins, which were thought to have a role in the penetration of the cercariae into the host skin<sup>2</sup>. *Spirometra erinaceieuropaei* plerocercoids produce and release prostaglandin E<sub>2</sub>, which may regulate host macrophage and lymphocyte functions<sup>3</sup>. Prostaglandins are thought to be involved not only in the defense mechanism against host immune systems, but also in the penetration and the migration mechanism that may cause sparganosis.

In general, Diphyllbothriid larvae in fish, which have lower temperature and lower AA concentration, don't cause sparganosis in humans. However, *S. erinaceieuropaei* plerocercoids do cause sparganosis in humans. What happens when the plerocercoid changes from a host of lower temperature to that of higher temperature, and from higher to lower AA concentration? The hamster has an AA/eicosapentaenoic acid ratio (A/E) of 1.76 in serum<sup>4</sup>, which is very similar to that of the human, 1.75 (Ref. 5); it is therefore a good animal model of sparganosis. *Diphyllbothrium hottai* from a fish changes the fatty acid composition during development from plerocercoid to adult in the hamster. The A/E, however, changed a little (from 0.5 to 0.39) in the 48 h post-infection in hamster intestines.

In contrast, A/E of *S. erinaceieuropaei* plerocercoid was 29.33 and 12 in the snake and hamster, respectively<sup>6</sup>. The A/E of *S. erinaceieuropaei* measured 0.34 in cat intestines, where the plerocercoid developed to adult. But the A/E in cat serum is 0.87 – much lower than that of the hamster or of the human. These results suggest that AA concentration and continuous AA supply in a host are important factors favouring sparganosis when the host temperature is high.

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## A Family of PP2 Phosphatases in *Plasmodium falciparum* and Parasitic Protozoa: Reply

The life cycle of *Plasmodium* is complex. Even within the sexual phase, there are a number of distinct developmental processes. These include: gametocytogenesis, formation of both male and female gametocytes, exflagellation (which results in the release of eight motile male gametes from a single male gametocyte); fertilization of the extracellular gametes; and ookinete migration and development. The mechanisms by which these events are controlled are not yet understood, but will involve precise interplay of signalling pathways.

We have recently isolated a number of genes from *Plasmodium falciparum* encoding enzymes potentially involved in signal transduction, all of which are expressed specifically in the sexual erythrocytic stages of the life cycle. These include two cyclases (D.J. Carucci et al., unpublished; A.A. Witney et al., unpublished) and two protein phosphatases (PfPP- $\alpha$ ; Ref. 1) (PfPP- $\beta$ ; Ref. 2). On the basis of structural comparisons, PfPP- $\alpha$  is most closely related to phosphatases in the type-1 subgroup whereas PfPP- $\beta$  shows greatest similarity to protein phosphatase type-2A (PP-2A).

The Comment article by Garcia et al. (this issue) discusses features of three serine/threonine phosphatase homologues from *P. falciparum*. The first is the unusual 'double' PfPP-2C that might be involved in a stress response, as it can complement the heat-shock response defect of a *Schizosaccharomyces pombe* strain with a PP2C deletion<sup>3</sup>. Second, the new putative type-2A phosphatase (MP03041) from the *P. falciparum* sequence database (Sanger Centre, Hinxton, UK) which, on the basis of amino acid sequence, is likely to be a PP-2A. MP03041 contains the sequence CYRCG, suggesting that it might be highly sensitive to okadaic acid<sup>4,5</sup>. Whether or not MP03041 is the okadaic-acid sensitive PP-2A that we alluded to previously<sup>2</sup> will require further experimentation. Several features of the third sequence PfPP- $\beta$  (Ref. 2) are worth re-emphasizing in the light of the Comment article. Database analysis of the C-terminal (catalytic) region of the molecule reveals greatest similarity (58% identity and 73% similarity) to *S. pombe* Ppa1. Disruption of the *ppa1*<sup>+</sup> gene together with the *ppa2*<sup>+</sup> gene (encoding another PP-2A-like phosphatase in fission yeast) has been shown to be lethal to *S. pombe*<sup>6</sup>. Analysis of the N-terminal region reveals that amino acids 53–99 exhibit 44% similarity and 27% identity to the corresponding region (amino acids 22–68) of *Saccharomyces cerevisiae* PPH22, a homologue of mammalian PP-2A. The molecule, therefore, might be most closely related to PPH22 of budding yeast which, together with another phosphatase, PPH21, is essential for growth<sup>7,8</sup>. Several potential phosphorylation sites are present in the

N-terminal segment of PfPP- $\beta$  including those for cAMP-dependent protein kinase and protein kinase C<sup>9</sup>, suggesting that the activity of PfPP- $\beta$  may be regulated by reversible phosphorylation of the N-terminal segment. The sequence of PfPP- $\beta$  contains the motif CYRCG, suggesting that it might also be highly sensitive to the inhibitor okadaic acid. However, our work has indicated that okadaic acid does not affect early gametocyte development *in vitro* (B.S. Hall et al., unpublished), implying that PfPP- $\beta$  might be involved in later sexual stage events.

It is known that PP-2A exists as a heterotrimeric holoenzyme composed of a common core structure associated with different regulatory subunits<sup>10</sup>. Clearly, identification and characterization of the potential regulatory subunits of PfPP- $\beta$  will give a greater understanding of the precise role of this molecule. In addition experiments are in progress (in collaboration with A.F. Cowman, Walter and Elisa Hall Institute, Melbourne, Australia) to disrupt the genes we have isolated, in order to investigate their roles in sexual development.

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### Erratum

In Tables 1 and 2 of the article entitled 'How do protozoan parasites survive inside macrophages?' by Christian Bogdan and Martin Röllinghoff (*Parasitol. Today* 15, 22–28, 1999), *Toxoplasma gondii* was spelt out as *Trypanosoma gondii*.

We apologize for this error.

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